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THE EFFECTS OF A THREE-WEEK ADAPTATION TO A LOW CARBOHYDRATE/ HIGH FAT DIET ON METABOLISM AND COGNITIVE PERFORMANCE

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SUMMARY

One of the principal metabolic adaptations to endurance training is an increase in the muscle's utilization of fat. This study investigated several components of metabolism during a three-week adaptation to a low (7-9%) carbohydrate/high (73-75%) fat diet (LCD) in man. Metabolic measurements were taken initially on ten healthy male volunteers, ages 19-41, on a maintenance exercise program while consuming a standard diet (STD) (50% carbohydrate/35% fat). These measurements were subsequently repeated after 7-11 and 17-21 days on the LCD. Questionnaires were administered on repeated occasions to evaluate food acceptability and subjective symptoms. The metabolic tests included intravenous glucose tolerance tests (GTT), meal response tests (MRT), and glucose/insulin clamps (CLAMP). Blood samples were also taken on several occasions during the STD and LCD periods to assess changes in overnight fasted blood glucose, free fatty acids, triglycerides, insulin, glucagon, cholesterol [total, high density lipoprotein (HDL), low density lipoprotein (LDL)], cortisol, thyroid hormone, electrolytes, and ketone bodies. The LCD was well-tolerated during the three-week adaptation period. The LCD produced lower blood triglycerides (-30%), glucose, thyroid hormone, and insulin/glucagon ratio. The LCD also elevated blood HDL-cholesterol, free fatty acids, and transiently elevated cortisol and ß-OH-butyrate. The MRT demonstrated markedly lower insulin, glucose, and triglyceride concentrations from consuming the LCD. The metabolic adaptation to the LCD resulted in unchanged insulin response to the GTT in the face of higher blood glucose during the test. The decrease in insulin sensitivity (glucose area/insulin area) indicated by the GTT was not confirmed by the CLAMP, which showed no change in insulin sensitivity. There was no change in muscle glycogen concentration after the three-week adaptation to the LCD. The alterations in metabolism demonstrated by this study are very encouraging for the use of the LCD as an adjunct to increasing certain types of exercise endurance, as well as for a potential treatment of several types of metabolic disorders.

INTRODUCTION

Military missions by Navy Special Warfare and Marine Corps personnel may require extended-duration work. Current dogma indicates diets high in carbohydrates (CHO) are the best means of achieving maximal performance. However, the preponderance of investigation in this area of exercise nutrition has focused on higher intensity exercise (competitive events) than that required for military personnel. Available information suggests that enhancing the capacity of the body to utilize fat as the primary energy source may substantially improve performance during the lower intensity and longer duration demands required during military missions.

Sustained work by military personnel during field operations requires less than 50% of maximal oxygen consumption (VO_2 Max). Many studies have demonstrated advantages in using CHO loading to improve high intensity (> 70% VO_2 Max) exercise endurance. However, the one-shot improvements in competitive exercise performance gained from CHO loading may not provide the best advantages for longer duration military applications. The ability to decrease CHO dependence and increase fat utilization during extended-work schedules could provide several advantages. These include: 1) greater energy reserves in the body as fat stores; 2) decreased ration weight (higher caloric density); 3) apparent natural shifts in metabolism to burn more fat when exposed to cold (25) or high altitude environments (personal communication); 4) increased caloric efficiency from food consumed (27); and 5) improvement in performance when insufficient calories are supplied to meet total metabolic requirements. A previous study in man demonstrated that adaptation to a 1% CHO/85% fat diet for four weeks resulted in maintenance of bicycle exercise endurance at 62-65% VO_2 Max (27). This study also reported greater utilization of fat for metabolic fuel, greater metabolic efficiency, lower muscle glycogen utilization (but lower glycogen content), and slightly lower blood glucose, higher insulin, greatly elevated blood ketone bodies, and lower blood triglyceride (TG) concentrations. Another non-exercise study which utilized a 15% CHO/70% fat diet for four weeks resulted in a similar lowering of blood TG concentration (1). Although exercise was not employed in this study, the lowering of blood TGs in face of elevated dietary fat intake suggests a metabolic adaptation similar to the 1% CHO/85% fat diet.

Our recent studies in exercise-trained pigs maintained on a 7% CHO/74% fat diet [low carbohydrate/high fat diet (LCD)] (12) demonstrated a 30% increase in moderate intensity (65% VO_2 Max) exercise endurance over the control diet pigs (74% CHO/7% fat). The LCD pigs as compared to control also demonstrated increased resting insulin and decreased TG concentrations, with only a slight elevation in blood ketone bodies, increased blood glucose during runs to exhaustion, no change in muscle or liver glycogen concentrations, and possibly decreased insulin sensitivity. The LCD adaptation promoted this shift to using fat as the primary energy source (27). The shift in metabolism in swine resulted in higher blood glucose concentrations throughout sustained moderate exercise (12). Since cerebral function is dependent on adequate availability of blood glucose, the LCD data suggest that cognitive performance may also be enhanced during selected missions by using the LCD. Other studies utilizing various low CHO diets for up to five days demonstrated decreased exercise endurance and cold tolerance. These data indicate that a period longer than five days of adaptation is required to achieve the desired benefit.

The purpose of this study was to explore the metabolic adaptations in man associated with the consumption of a low CHO/high fat diet during a closely supervised three-week period. The design incorporated the measurement of selected alterations in metabolic variables, cognitive performance, and maximal exercise capacity. These measures were repeated during a Standard Diet (STD) period and at four, time points while consuming the LCD (2, 4, 8-11, and 18-22 days). The objective of this study was to describe more fully the nature and time course of the metabolic adaptations which occurred.

METHODS

The general approach required the evaluation of several variables during a baseline period, while consuming a standard diet (STD), and during a 21-day adaptation to a real food, low carbohydrate/high fat diet (LCD) (7-9% carbohydrate/73-75% fat). Repeated measures were performed on 10 healthy male volunteers, with full informed consent, between the ages of 19 and 41 years, and who were on a maintenance exercise training program. The variables measured during the STD (50% carbohydrate/35% fat) and LCD dietary periods

included multiple blood samples obtained between 0715 and 0800 at rest (with no prior exercise) and after an overnight fast, maximal exercise tests, computerized performance assessment batteries (PAB) by Essex, 72-hour urine and stool collections, and four dynamic tests used to evaluate metabolic function. In addition, daily questionnaires and frequent medical evaluations were used to determine acceptability of the food and any possible negative effects from consumption of the LCD. These measurements allowed for the evaluation of blood borne energy substrates and hormones, as well as changes in selected intracellular (muscle) enzymes.

The variables used as indicators of the changes in metabolism included blood glucose, insulin, glucagon, cortisol, thyroid function, triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), ketone bodies, and electrolyte concentrations, as well as urine analysis for pH, ketone bodies, and specific gravity. The dynamic tests included standard intravenous glucose tolerance tests (IV-GTT), IV fat tolerance tests (IV-FTT), meal response tests (MRT), breakfast response tests (BRT), and glucose/insulin clamps (CLAMP). The IV-GTT measured the standardized insulin response to a standard intravenous glucose load (330 mg/kg) the injected quantity of glucose and the rate of disappearance of glucose from the blood (22). The IV-FTT, in a manner similar to the IV-GTT, measured the kinetics of removal of an injected triglyceride emulsion (Intralipid^{R}) preparation (6). The MRT was used to demonstrate alterations in blood glucose, insulin, triglycerides, and free fatty acids in response to the consumption of the STD and LCD meals during a normal day without exercise. The CLAMP procedure measured insulin sensitivity changes in both peripheral and hepatic tissues. An associated muscle biopsy was used to determine muscle glycogen content and intracellular enzyme activities of pyruvate dehydrogenase (PDH) and glycogen synthetase (GS). Concurrent indirect calorimetry measurements quantified rates of oxidation and nonoxidative (storage) glucose metabolism. Computerized PAB testing included reaction time, reasoning, code substitution, calculations, mood, and memory as measures of cognitive function (9).

OVERALL SCHEDULE. The protocol for each subject was segmented into four phases (Appendix A). As outpatients, the first two phases were carried out

by the subjects at the Clinical Research Center (CRC) facility of the University of California, San Diego, Medical Center. **Phase** I consisted of a suitability interview, which included general health and family history, current dietary practices, and exercise practices. If the subject was suitable for the study and was interested, he received and signed the approved Informed Consent, was given a complete Medical History and Physical Examination by a qualified physician, and had preliminary morning blood and urine samples analyzed for standard biochemical profiles. During **Phase** II, which generally lasted about three weeks, the subjects reported to the CRC to receive: 1) Intralipid^{R} test dose (see IV-FTT); 2) forms and instructions for maintaining an exercise record; 3) forms and instructions for completing a standard prospective diet record; 4) review and analysis of diet records; 5) five sessions of introduction and practice on taking the computerized PAB; 6) the STD grocery list, schedule, and funds to buy food for one week prior to admission (Phase III); and 7) review and adjustment (if needed) of the caloric level of the diets based on changes in body weight.

After one week on the STD, **Phase** III began by admission to the CRC. All food was prepared and measured in the CRC kitchen to ensure proper portions and composition. Investigators verified that subjects consumed all of the food presented to them, and food was either consumed at the CRC or was packed for outside consumption during the subjects' daily activities (not study-related). All meals were consumed prior to 2000 hours each evening. Subjects were requested to be in bed no later than 2230 hours on those nights when in the CRC unit prior to the next morning's testing. The same procedures were followed during the LCD (Phase IV). During the approximately eight-day hospital admission for Phase III and while being maintained on the STD, subjects completed: 1) a maximal cycle exercise test; 2) IV-GTT; 3) IV-FTT; 4) BRT; 5) MRT; 6) a submaximal cycle exercise test; 7) "Food Questionnaires" for three days (Appendix B); 8) daily subjective symptomatology questionnaire ("Daily Diary," Appendix C); 9) morning's first void urine collections; 10) 72-hour collections of urine and stool; and 11) CLAMP and muscle biopsy. **Phase** IV of the study required the exclusive consumption of the LCD meals, which began from one to 30 days after the completion of the STD Phase III testing. Blood and urine samples, as well as questionnaires, were obtained after two and four days on the LCD (LCD 2-4). All of the tests

performed during Phase III were repeated in the course of the 21-day CRC admission during two time periods: after 7-11 days (LCD 7-11) and 17-21 days (LCD 17-21) on the LCD (except for the CLAMP/biopsy which was performed only during the LCD 17-21 period). This collection scheme resulted in repeated measures of either three or four times for each variable. Since it was thought that there might be some interactive influence on the results obtained during the LCD period between the IV-GTT and the CLAMP, the order of these two tests was randomized.

DIET COMPOSITION. The diets were designed based on the information contained in the "Nutritionist 3" computerized dietary analysis program (N^2 Computing, Inc.). Individual average daily caloric intakes for the duration of the study were determined by a combination of the analysis of a three-day (Thursday, Friday, and Saturday) prospective diet record and an age/activity nomogram. The average daily composition during the STD Period was 48-53% Carbohydrate, 35-36% Fat, and 12-16% Protein. During the LCD period, the subjects consumed 7-9% Carbohydrate, 73-76% Fat, and 16-20% Protein. The diets were tailored to a seven-day rotation schedule. Samples of one complete day for both the STD and for the LCD are shown in Appendix D.

DAILY SCHEDULE. Subjects were required to sleep overnight at the CRC when testing was scheduled for the next day. Otherwise, they were allowed to check out overnight after eating dinner. When subjects slept at the CRC, they were awakened no later than 0700 for the taking of vital signs, urine samples, and body weight. No exercise was allowed for at least 24 hours prior to any testing. When scheduled, the PAB was commenced as close to 0700 as possible. Fasting blood samples (when scheduled) were started as close to 0730 as possible. Other tests involving blood sampling and/or exercise were started as close to 0800 as possible. No food was consumed (unless as a part of the test, e.g., BRT and MRT) until after the completion of each test.

INDIVIDUAL TEST PROTOCOLS. At least 20 minutes prior to beginning the tests, and in all protocols where blood samples were required, a plastic IV catheter was inserted into a vein located in the forearm or hand. Catheter patency was maintained by a saline drip without heparin. The IV-GTT consisted of two, baseline blood samples at 20 minutes and 1 minute prior to the injection

of 330 mg/kg of glucose as $D_{50}W$. The same absolute dose was used for all three IV-GTT's performed regardless of any recorded changes in body weight. Post-injection blood samples were obtained at 2, 4, 6, 8 ,10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, and 180 minutes. All samples were analyzed for glucose and insulin (see biochemical analyses). Based on previous data, an alteration in the responses of glucose and insulin as a result of adaptation to the LCD, was anticipated (12). These three identical tests allowed the comparison of data during all three time periods (STD, LCD 7-11, and LCD 17-21) of the study.

The IV-FTT utilized the injection of Intralipid^R, an intravenous triglyceride emulsion preparation. The test is designed to measure the pattern of disappearance of the triglyceride injected (6). Due to a low incidence of reported allergies to Intralipid^R, a test dose of 0.1 ml/min infused for 15 minutes was implemented during Phase II to ensure subjects were not allergic to the preparation. The actual IV-FTT consisted of a baseline blood sample, followed by the injection of 0.10 ml/kg of Intralipid^R 10% solution. This injected amount of Intralipid^R was somewhat less than what had originally been described (6). Post-injection samples were obtained at 5, 10, 15, 20, 30, 45, and 60 minutes. All samples were analyzed for total triglycerides and total free fatty acids (see biochemical analyses). The same absolute dose of Intralipid^R was used for all three tests.

The MRTs were used to define the blood substrate (glucose, free fatty acids, triglycerides) and insulin responses to consuming breakfast and lunch during a normal day. This response was considered to be both the stimulus to, and the result of any alterations in patterns which occur as a result of adaptation to the LCD. The MRT required: 1) a baseline blood sample (t = 0); 2) the consumption of a breakfast meal completely within 20 minutes; 3) blood samples every 30 minutes for five hours (t = 300); 4) consumption of a second meal within 20 minutes; and 5) continuation of the 30-minute blood samples for four additional hours (t = 540). Subjects were not allowed out of bed, except for toilet visits, during the first three hours of the test. The two meals eaten during each test were composed of the STD food during the STD period (Phase III) and the LCD food during the LCD period (Phase IV). Since there could be a change in how the body's system metabolically handled

the LCD food consumed, the BRT was conceived to allow the comparison of identical LCD meals during all three time periods (STD, LCD 7-11, and LCD 17-21) of the study. The BRT, administered only during the STD period, was identical to the MRT, except the test was terminated after the five-hour sample (t = 300) and the meal consumed was a LCD meal. The addition of the BRT allowed the comparison of the response to the same meal during both the STD and LCD periods. The MRT and BRT blood samples were analyzed for glucose, insulin, and free fatty acids at every time point. In addition, the samples for baseline, 30, 60, 90, 120, 150, 180, and hourly, thereafter, were analyzed for total triglycerides (see biochemical analyses).

The CLAMP test followed the procedures of DeFronzo et al. (7) to determine glucose uptake or disposal rate and insulin sensitivity. The complex procedure involved the infusion of ^{3}H-3-glucose (6 μCi$\cdot$min^{-1} as a tracer during a two-hour baseline period. During this period, the subject remained at rest while frequent blood samples were taken to determine baseline glucose, insulin, and glucagon concentrations. After this two-hour reference (basal) period, a vastus lateralis muscle biopsy using sterile anesthetic procedures was obtained via a Bergstrom muscle biopsy needle (2). The muscle tissue was rapidly frozen in liquid nitrogen for later analysis of glycogen, PDH, and GS (see biochemical analyses). At the completion of the biopsy procedure, and with the continued infusion of ^{3}H-3-glucose tracer, an infusion of insulin at a rate of 40 mU$\cdot$(M$^{2}\cdot$min)$^{-1}$ was initiated. The infusion of insulin resulted in the simultaneous shut-down of endogenous glucose production by the liver and increased glucose uptake by insulin sensitive tissues. In order to maintain blood glucose levels at 90 mg% under these insulin-stimulated conditions, a variable rate infusion of $D_{20}W$ was employed. During the remainder of the three-hour infusion, the insulin infusion was maintained at a constant rate, while the glucose infusion rate was adjusted to maintain a constant blood glucose concentration. This artificial external control of insulin and glucose concentrations provides the term "clamp" after which the procedure was named. After the three-hour CLAMP was completed, a second (stimulated by the elevated insulin in the blood) muscle biopsy was obtained for the same analyses as listed for the first. At the end of both the basal and stimulated periods of the CLAMP, the glucose disposal rate (GDR) and hepatic glucose output (HGO) were measured.

Glucose and lipid oxidation were determined by indirect calorimetry (Deltatrac by Sensormedics, Inc.) during the last 40 minutes of the basal and stimulated periods. The averages of oxygen consumption and carbon dioxide production were used to calculate glucose and fat oxidation by the equations of Frayn (11). The rates of non-oxidative glucose metabolism, reflective of glucose storage, were estimated by subtracting the rates of glucose oxidation from overall glucose disposal rates. The entire CLAMP procedure was performed during the STD period and at the end of the LCD adaptation period.

The collection of stool samples was initiated at 0600 on Day-1, with all stool collected during the next 72-hour period for each of the testing periods. The stool samples were collected directly into paint-type metal cans. The cans were kept frozen at -30°C. After the collection, the samples were weighed, thawed, a small amount of water added to facilitate homogenization, re-weighed, and shaken in a standard agitator-type paint mixer for at least 10 minutes. Homogenized samples were aliquoted into sealed plastic storage containers and frozen at -30°C for later analyses of quantitative fecal fat and nitrogen. To ensure that neither the change in diets nor the alteration in their daily schedule adversely affected the stool collections, 100 mg Colace^{R} (docusate sodium) was administered each morning. Due to unusually high fecal fat concentration measured during even the STD period, we postulated that the Colace^{R} was either causing or contributing to high fecal fat content. To test this hypothesis, we discontinued the use of Colace^{R} in five subjects immediately after stool collection obtained during the LCD 7-11 period. Thus, those five subjects received Colace^{R} for the STD and LCD 7-11 periods, but <u>not</u> during the LCD 17-21. The fecal fat results will be reported here, but the fecal nitrogen will be reported separately.

During the same three, 72-hour periods, the stool samples were collected; three, consecutive 24-hour urine collections were also obtained. The urine was collected directly into plastic containers containing preservative and refrigerated at 2°C. The collections were initiated at 0600 on one day and completed at 0600 on the following day. After the samples were collected, alliquots were frozen for later quantitative analyses for creatinine and nitrogen. Those results will be reported separately in another publication.

Maximal Exercise Tests were performed on each subject on three occasions (see above) during the study, and will also be reported in a separate publication.

The computerized PAB (by Essex) was administered on a Zenith Z-184 portable lap top computer. The tests were taken in the same order, and each session was at approximately the same scheduled time each day (0630-0700). The subjects were given one introductory session to learn the procedures and five training sessions to reach purported plateaus in skill (9). The tests were repeated 12 additional times during the study. The results and details of the testing will be reported in a separate publication.

Two questionnaires were used during the study. A "Food Questionnaire" (Appendix B) was completed three times during the STD period (Phase III), and seven times during the LCD period (Phase IV), once after two days, and three times each during the 7-11 day and 17-21 day periods on the LCD. The Food Questionnaires were used to evaluate subjective feelings of hunger, satiety, and preferences for the food presented to them while on the respective diets. The same set of 10 questions was presented to the subject for each of the three meals during the 10-separate-days period covered by the questionnaire. The numerically-weighted responses of each subject were averaged over all of the questionnaires which individuals completed during the four respective periods. The responses of subjects were then compared for the STD and LCD periods using repeated measures analyses to determine if there were any differences between their responses to individual questions. Individual comments were noted.

The "Daily Diary" (Appendix C) was completed daily and used to obtain subjective assessments of well-being and symptomatology. The 32 questions from the "Daily Diary" were analyzed to determine the frequency of responses for each question (including, "NO Problems"), the percentage of days for which non-zero responses were recorded, and the average severity of the symptoms recorded. Numerical weights, attributed to each answer, are listed as "POINTS" (not shown on the actual forms) in Appendix C. Responses to each question for individual subjects were averaged for all of the questionnaires completed during the respective periods of the STD period and for four

segments within the LCD period (Days: 1-5, 6-10, 11-16, and 17-22). The responses of subjects to each question were then compared using repeated measures analyses to determine if there were any differences in the frequency or severity of complaints recorded during the respective periods.

BIOCHEMICAL ANALYSES. Within 15 seconds after being withdrawn from the vein, blood samples obtained for the various analyses were placed in collection tubes. Glucose samples were either analyzed immediately or saved on ice and in sodium fluoride tubes for later analysis. Insulin, cortisol, thyroid function, and electrolytes samples were placed in siliconized tubes and allowed to clot. Triglycerides, Cholesterol, HDL, LDL, and free fatty acids were placed in EDTA tubes and immediately iced. Glucagon was placed into tubes containing 50 μl of Trasylol per ml sample (Mobay Pharmaceutical, New York, New York) and iced immediately. After the initial treatment, all of the samples were centrifuged at $2^{o}C$, the serum transferred into poylpropylene freezer tubes, sealed, and rapidly frozen at $-70^{o}C$. Samples were later analyzed by techniques listed below.

Blood glucose and lactate were analyzed using the Yellow Springs Instruments automated Glucose/Lactate Analyzer (Model 23L). Insulin was analyzed by the Rubenstein method (17). Glucagon was analyzed by the Unger method (35). Free fatty acids were determined by the colorimetric ultramicro method (24). Total triglycerides were measured using A-gent^{R} reagents (Abbott Labs, South Pasadena, California) for determination of enzymatically-liberated glycerol using glycerol kinase. Total cholesterol was determined using reagents (Boehringer-Mannheim Diagnostics, Indianapolis, Indiana) which accomplished enzymatic hydrolysis of cholesterol esters. The HDL fraction of cholesterol was determined using the same process as for total cholesterol, except the analysis was performed after the HDL fraction was precipitated from the plasma by heparin and manganese. The LDL fraction of cholesterol was computed using the Friedenwald Equation which estimates the very low density lipoprotein cholesterol (VLDL) as being 20% of the triglyceride concentration, with [LDL] = ([Total Cholesterol] - [HDL] - [VLDL]). Total thyroxine (T_4) and thyroid-stimulating hormone (TSH) were measured using fluorometric Enzyme Immunoassay (Baxter, Miami, Florida) and triiodothyronine (T_3) was determined by radioimmunoassay (Monobind, Costa Mesa, California).

Cortisol was determined by radioimmunoassay technique (16). Blood ketone bodies (ß-OH-butyrate) were measured by enzymatic oxidation (37). Wet weight muscle glycogen (μmole·gm^{-1}) was determined flurometrically as glucose units after HCl hydrolysis as described by Passonneau and Lauderdale (26).

Extraction of muscle for enzyme assays (PDH and GS) were performed using a modification of the methods of Hagg et al. (14). Muscle samples of approximately 50 mg were weighed while frozen and immediately homogenized in an iced buffer consisting of 2.0 mM dithiothreitol (DTT), 20 mM NaF, 2 mM EDTA, and 50 mM potassium phosphate at a pH of 7.4. Fluoride was included to inhibit PDH phosphate (36) in order to maintain PDH in its in situ phosphorylation state. All steps were performed at 4°C. Homogenization was accomplished with a polytron homogenizer (Brinkman Instruments, Westbury, New York). The crude extract was then divided into two tubes and centrifuged at 20,000 g for 20 minutes and the supernatant discarded. A portion of the resulting pellets were suspended in 2 ml of the same buffer, while the remaining portion was suspended in the buffer without NaF. The pellets were again centrifuged at 20,000 g and the supernatants discarded. Removal of the NaF allowed the activation of PDH by high magnesium concentration, presumably through activation of PDH phosphatase. The resulting pellets were homogenized for 10 seconds in 0.75 ml of the same buffers, except for the addition of 0.2% Triton X-100 to solubilize mitochondrial membranes to allow free access of substrates to the enzyme. Protein content of these extracts were determined by the method of Lowery (18). PDH assays were performed by a modification of the method of Hagg et al. (14), based on the technique of Blass et al. (3). Glycogen Synthetase (GS) was assayed by a modification of the method of Thomas et al. (33). Maximal activity of GS was determined at saturating concentrations of G-6-P (10 mM) and UDPG (5 mM). The activity of GS was expressed as nMoles of UDPG incorporated into glycogen per minute per mg of extract protein. Performing the assay with a range of G-6-P concentrations allowed the determination of the $A_{0.5}$ for G-6-P (the concentration of G-6-P that half maximally stimulates GS). The activity of GS assayed at 0.1 mM G-6-P divided into the activity of GS at 10 mM G-6-P is termed the fractional velocity ($FV_{0.1}$), a sensitive measurement of changes in GS activity.

Daily morning urine samples were tested using a Multistix^{R} (Miles, Inc., Elkhart, Indiana) to measure pH, glucose, protein, and ketone bodies, while a standard urinometer was used to measure specific gravity. Quantitative ketone contents from the dipstick measurement were assigned the following scores for comparative analysis: Negative = 0; Trace = 1 ($5mg \cdot dl^{-1}$); Small = 2 ($15mg \cdot dl^{-1}$); Moderate = 3 ($40mg \cdot dl^{-1}$); High = 4 ($80mg \cdot dl^{-1}$). From the scores for each variable grouped by the STD and three LCD periods, individual mean values were computed for each period, and evaluated using repeated measures analysis.

Three-day stool collections for quantitative fecal fat obtained during the STD, LCD 7-11, and LCD 17-21 periods were analyzed using the techniques described by Henry (15). Denatured ethanol (5 ml) and petroleum ether (20 ml) were added to alliquots of emulsified and acidified specimens. The mixture was centrifuged and the supernatant containing the various species of fats were separated. The supernatant was then evaporated and the weight of the residual (fat) was weighed. The results were then expressed as the amount of fat contained in the timed stool samples ($gm\ fat \cdot 24\ hrs^{-1}$).

Three, consecutive, 24-hour urine collections obtained for measurement of quantitative creatinine and nitrogen, as well as three-day stool collections for quantitative nitrogen have not been completed and will be reported later in a separate publication.

ADDITIONAL CALCULATIONS. For each of the timed tests (IV-GTT, IV-FTT, MRT, BRT), the Total Area under each plot of the results (e.g., Y-axis: glucose concentration, and X-axis: time) was calculated using the sum of the trapezoid approximation of the areas between successive data points. This technique does not utilize any curve smoothing or fitting techniques. In addition to this Total Area, an Adjusted Area was also computed. The Adjusted Area was defined as the area above the baseline (initial) value for the individual variable.

STATISTICS. Since each subject completed all of the tests, SPSS-X was used to compute a repeated measures analysis of variance (ANOVA) to define patterns of change across time. Individual differences between time points

were determined by simple contrasts (31). Each variable was analyzed using either three times (t1 = STD period, t2 = LCD 7-11, t3 = LCD 17-21) or four times (t1 = STD period, t2 = LCD 2-4, t3 = LCD 7-11, t4 = LCD 17-21) as the within subject variable. The variables recorded more than one time for a given time period were averaged (e.g., mean of the resting blood glucoses obtained three times during the LCD 7-11 period) and analyzed using four times (t1 = STD period, t2 = LCD 2-4, t3 = LCD 7-11, t4 = LCD 17-21) as the within subject variable. The CLAMP data used a similar repeated measures with two times (t1 = STD period, t2 = LCD 17-21) as one within subject variable and two treatments (1 = Basal, 2 = post-CLAMP) as a second, within subject variable.

RESULTS

In general, the low carbohydrate/high fat diet (LCD) was well-tolerated, and the results were consistent with our expectations. There were no significant difficulties encountered from either the extensive testing or consumption of the LCD. The results of the various biochemical samples obtained on specific days during the study are listed in Table 1. All values are reported as MEAN ($\pm$ Standard Deviation). Any changes reported are significant at the $p < .05$ level, unless otherwise stated.

There was a decline in resting blood glucose only at the LCD 7-11 period. There was also a decline in blood triglycerides, while the high density lipoprotein (HDL) fraction of cholesterol was increased at all LCD time periods. Thyroxine (T_4) was increased at LCD 2-4, whereas triiodothyronine (T_3) was decreased at LCD 17-21. Although the blood ketone (ß-OH-butyrate) concentrations were increased slightly throughout the LCD period, the increases were only significant during the LCD 7-11 period. One subject, who frequently had negative ketones in the urine, did have elevated blood ketones indicating a higher threshold for spillage. Although blood pH was not measured, the decline in blood HCO_3^- may reflect correction of the chronic metabolic acidosis from the elevated blood ketone bodies. The metabolic status was confirmed by a decline in urine pH from 6.45 ($\pm$ 0.55) during the standard diet (STD) period to 5.10 ($\pm$ 0.21) by the end of the LCD period and

Table 1. Fasting biochemical variables measured during the Standard Diet (STD) and at three times during a 21-day adaptation to a low carbohydrate/high fat diet (LCD).

	STD PERIOD		LCD PERIOD					
Variable			Days 2-4		Days 7-11		Days 17-21	
Glucose	89.3	(5.2)	87.9	(3.4)	82.7	(6.6)a	89.0	(6.9)
TG	81.9	(42.8)	56.9	(20.6)	52.2	(18.7)a	46.9	(14.3)a
% of STD TG	100.0	—	76.4	(25.0)a	69.4	(18.9)a	66.4	(31.2)a
FFA	0.43	(0.12)	0.47	(0.12)	0.64	(0.17)a	0.61	(0.17)a
Insulin	7.6	(4.3)	7.7	(4.2)	4.9	(1.7)	5.2	(3.6)
Glucagon	112.8	(27.9)					133.5	(45.0)
I/G Ratio	0.049	(0.024)					0.023	
(0.010)a								
Total CHOL	156.5	(19.1)	168.7	(27.4)	167.8	(22.4)	167.6	(28.9)
LDL-CHOL	93.5	(17.5)	100.5	(20.2)	103.9	(21.5)	104.8	(24.0)
HDL-CHOL	46.6	(10.4)	56.0	(17.6)a	55.0	(14.7)a	52.3	(15.0)a
Cortisol	91.4	(27.7)	173.7	(21.1)a	127.3	(46.8)ab	105.1	(36.8)b
TSH	2.2	(0.9)	3.2	(2.1)	2.4	(1.1)	2.2	(1.6)
T_4	6.0	(0.8)	6.8	(1.3)a	6.8	(0.6)a	5.3	(1.6)
T_3	119.8	(12.8)	149.4	(82.1)	107.7	(12.9)	85.9	(8.1)a
Na^+	139.1	(1.4)	142.0	(3.8)	138.3	(1.7)	139.2	(1.8)
K^+	4.3	(0.1)	4.7	(0.5)a	4.5	(0.2)a	4.2	(0.2)
HCO_3^-	30.5	(4.3)	30.7	(5.8)	28.3	(3.9)	25.6	(4.7)a
Cl^-	105.4	(1.8)	107.7	(4.7)	105.9	(1.5)	105.6	(2.0)
B-OH-But	4.3	(3.0)	6.6	(2.1)	11.2	(4.2)a	7.4	(6.6)

Values reported for ten subjects (n = 10): **MEAN (Standard Deviation)**. Units: Glucose ($mg \cdot 100ml^{-1}$); Total Triglycerides (TG) ($mg \cdot dl^{-1}$); % Chng TG = -[(STD period TG)-(LCD period TG)]/(STD period TG)·100 (% difference from STD value); Total Free Fatty Acids (FFA) ($mmol \cdot l^{-1}$); Insulin ($\mu U \cdot ml^{-1}$); Glucagon ($pGm \cdot ml^{-1}$); Total Cholesterol (Total CHOL) ($mg \cdot dl^{-1}$); Low Density Lipoprotein (LDL-CHOL) ($mg \cdot dl^{-1}$); High Density Lipoprotein (HDL-CHOL) ($mg \cdot dl^{-1}$); Cortisol ($\mu Gm \cdot l^{-1}$); Thyroxine (T_4) ($\mu Gm \cdot dl^{-1}$); Thyroid Stimulating Hormone (TSH) ($\mu IU \cdot ml^{-1}$); Triiodothyronine (rT_3) ($ng \cdot dl^{-1}$); Sodium (Na+) ($mmol \cdot l^{-1}$); Potassium (K^+) ($mmol \cdot l^{-1}$); Bicarbonate (HCO_3^-) ($mmol \cdot l^{-1}$); Chloride (Cl^-) ($mmol \cdot l^{-1}$); Beta-hydroxy-butyric acid (B-OH-But) ($mg \cdot dl^{-1}$). Statistical Differences noted $p < .05$, with 'a' denoting difference from the STD Period value and 'b' difference from LCD Days 2-4 period.

a corresponding increase in urine ketone bodies from Negative to a score of +1.5 (± 0.8), which is approximately equivalent to 10 (± 4) $mg \cdot dl^{-1}$.

The amount of fat excreted in the feces during the Standard Diet (STD) period was 6.2 (± 2.9) gm fat·24 hrs^{-1} (n = 9). The normal value is less than 7.0 gm. One subject was excluded due to a mild case of diarrhea (attributed to a non-related illness) experienced during the STD period stool collection. The fecal fat excretion increased during the first LCD period (7-11 days) to 21.3 (± 11.4). Three of the subjects had markedly higher fecal fat excretion [44.3 (± 13.1)] than did the other seven [16.4 (± 5.1)], however, all were elevated. All subjects had been maintained on daily Colace up to this time. During the last LCD period (17-21 days), the five subjects who remained on Colace continued to demonstrate elevated fecal fat excretion [25.4 (± 13.2)], while five who had been removed from the Colace reverted to normal values [6.8 (± 1.8)]. In consideration of a potential relationship between excessive weight loss and excessive fecal fat excretion, a regression was performed using the fecal fat excretion during the first LCD period (7-11 days) and the computed percent of total body weight loss during the LCD period. There was a strong correlation (R = 0.93) which yielded the relationship: % change in body weight = 0.37 + 0.078·(fecal fat output).

In spite of being maintained on a eucaloric diet during the LCD period, and with no changes in activity level, there was decline in body weight from the STD period [80.3 (±8.2) Kg] to the LCD 2-4 [79.8 (± 8.2) Kg] and LCD 7-11 [79.3 (± 8.1) Kg] periods, with a further significant decline (from LCD 2-4) at the LCD 17-21 period [78.4 (± 7.9)]. However, there were some interesting subdivisions of the overall data. The three subjects with the highest fecal fat output (range: 30.3 to 56.2 gm·24 hrs^{-1}) demonstrated the greatest weight loss (Range: 3.0 to 5.1% of total body weight, or 2.0 to 4.5 Kg). The remaining seven subjects exhibited a 1.6 (± 0.6) % change in total body weight, or an average loss of 1.3 (± 0.5) Kg during the LCD period.

The stimulus for the metabolic adaptations to the LCD are illustrated in the results to the Meal Response Test (MRT) (Table 2). During these tests, the individuals consumed the STD meals during the STD period and the LCD meals during LCD period for the two meals administered during the tests. The

Table 2. Responses of biochemical variables to the Meal Response Test (MRT) measured during the Standard Diet (STD) and at two times during a 21-day adaptation to a low carbohydrate/high fat diet (LCD).

		STD PERIOD	LCD Period	
Variable	N		Days 7-11	Days 17-21
Maximal Values:				
Glucose	9	132.8 (23.2)	107.0 (16.3)a	105.6 (12.2)a
Insulin	9	111.0 (35.5)	30.0 (17.7)a	22.0 (10.0)a
TG	9	204.0 (113.0)	174.6 (57.8)	149.6 (42.9)
FFA	9	0.47 (0.12)	0.87 (0.16)a	0.78 (0.18)a
TOTAL Areas:				
GLU (x1000)	9	51.9 (2.7)	47.8 (1.8)a	48.7 (5.2)
INS (x1000)	9	19.0 (6.0)	6.1 (2.0)a	5.2 (1.6)ac
TG (X1000)	9	80.0 (44.4)	55.5 (17.4)a	50.6 (15.1)a
FFA	9	161.9 (28.5)	327.3 (63.1)a	301.0 (60.1)a
ADJUSTED Areas:				
GLU (x1000)	9	4.2 (3.3)	0.1 (2.6)a	0.9 (5.8)a
INS (x1000)	9	15.5 (5.3)	2.6 (1.6)a	1.7 (1.3)ac
TG (x1000)	9	39.5 (33.3)	15.1 (16.4)a	10.1 (11.5)a
FFA	9	-61.8 (61.0)	103.7 (73.5)a	77.4 (65.0)a

Values reported: MEAN (Standard Deviation) for the number of subjects (N) as indicated. Units: Glucose ($mg \cdot 100ml^{-1}$); Insulin ($\mu U \cdot ml^{-1}$); Total Triglycerides (TG) ($mg \cdot dl^{-1}$); Total Free Fatty Acids (FFA) ($mmol \cdot 1^{-1}$). Area Units: Glucose (GLU) (mg GLU·Min·$100ml^{-1}$); Insulin (INS) (μU INS·min· ml^{-1}); Total Triglycerides (TG) (mg TG·min·dl^{-1}); Total Free Fatty Acids (FFA) (mmol FFA·min·1^{-1}); Total Free Fatty Acids (FFA) (mmol FFA·min·1^{-1}). Statistical Differences noted $p < .05$, with 'a' denoting difference from the STD Period value and 'c' difference from LCD Days 7-11 period.

maximal values of glucose and insulin are somewhat less for the LCD periods than for the STD period. Corresponding to these declines in maximal values are reductions in the integrated response over the entire day (Areas) for glucose and insulin. There was an astonishing decline in the maximal and integrated responses to blood triglycerides (TG) during the LCD period, with a corresponding increase in maximal and integrated free fatty acids (FFA) responses. The negative value for the STD period Adjusted Area of FFA is reflective of a normal decline in FFA postprandially as a result in the increased circulating insulin concentrations.

The results of the Breakfast Response Test (BRT), which involved the consumption of the same LCD breakfast during all three time periods are shown in Table 3. These results suggested an adaptive response to consuming the LCD meal as illustrated by a decline in the insulin Total Area. However, this decline was not significant when corrections were made for changes in the baseline (resting) concentrations of insulin.

The responses to the repeated intravenous glucose tolerance tests (IV-GTT) are listed in Table 4. The results indicate an increase in the integrated glucose response for both Total and Adjusted Areas during the LCD with no change in the integrated insulin response. This is further illustrated by a reduction in the rate of decline of blood glucose (SLOPE: GLU) and two-fold increase in the integrated glucose (GLU Area) divided by the integrated insulin response (INS Area) reported on the table as G/I RATIO. These data indicate a marked alteration in the pattern of response to identical biochemical challenges.

The data obtained from the CLAMP testing is reported in Table 5. Glucose disposal rate during both the basal and insulin stimulated states were unaffected by diet. Lipid oxidation was not significantly changed during the basal period, however, it was significantly higher for the insulin stimulated portion of the CLAMP during the LCD than during the STD period. Glucose oxidation was significantly decreased during the LCD period in both the basal and insulin stimulated states. In agreement with this, measurements of pyruvate dehydrogenase (PDH) activity were significantly lower during the LCD in both the basal and insulin-stimulated phases of the CLAMP. The LCD also

Table 3. Responses of biochemical variables to the Breakfast Response Test (BRT) measured during the Standard Diet (STD) and at two times during a 21-day adaptation to a low carbohydrate/high fat diet (LCD).

Variable	N	STD Period	LCD Period Days 7-11	LCD Period Days 17-21
Maximal Values:				
Glucose	9	97.7 (6.6)	104.6 (17.7)	102.1 (11.4)
Insulin	9	24.4 (9.2)	22.7 (12.0)	21.3 (10.5)
TG	9	111.0 (45.0)	112.6 (38.3)	99.1 (35.1)
FFA	7	0.49 (0.08)	0.74 (0.18)a	0.69 (0.12)a
TOTAL Areas:				
GLU (x1000)	9	26.5 (1.4)	26.7 (1.6)	27.2 (3.1)
INS (x1000)	9	3.7 (0.9)	2.7 (1.1)a	2.8 (1.1)a
TG (x1000)	9	26.9 (10.1)	24.5 (7.9)	21.9 (6.4)
FFA	9	107.9 (12.7)	168.4 (43.9)a	159.8 (25.7)a
ADJUSTED Areas:				
GLU (x1000)	9	-0.0 (1.6)	2.2 (2.2)	0.5 (2.7)
INS (x1000)	9	1.7 (0.7)	1.3 (0.8)	1.2 (0.8)
TG (x1000)	9	4.5 (7.3)	10.4 (4.6)	7.9 (4.3)
FFA	9	-15.6 (34.3)	-14.2 (44.8)	-31.4 (38.6)

Values reported: MEAN (Standard Deviation) for the number of subjects (N) as indicated. See Table 2 for additional information.

Table 4. Responses of biochemical variables to the Intravenous Glucose Tolerance Test (IV-GTT) measured during the Standard Diet (STD) and at two times during a 21-day adaptation to a low carbohydrate/high fat diet (LCD).

Variable	N	STD Period	LCD Period	
			Days 7-11	Days 17-21
Maximal Values:				
Glucose	9	273.9 (61.5)	287.9 (17.1)	281.8 (31.3)
Insulin	9	111.3 (48.0)	97.1 (34.5)	103.0 (35.2)
TOTAL Areas:				
GLU (x1000)	9	18.5 (0.8)	21.8 (1.1)a	22.9 (2.4)a
INS (x1000)	8	2.7 (0.6)	2.3 (0.7)	2.5 (0.8)
ADJUSTED Areas:				
GLU (x1000)	9	2.3 (0.8)	6.9 (1.6)a	6.8 (1.7)a
INS (x1000)	8	1.1 (0.5)	1.4 (0.6)	1.6 (0.7)
SLOPE:				
GLU	7	-4.87 (1.42)	-3.15 (0.41)a	-3.71 (1.03)a
INS	10	-2.17 (2.34)	-0.93 (1.70)a	-1.15 (1.82)a
G/I RATIO:	8	2.51 (1.62)	5.78 (2.43)a	4.81 (2.27)a

Values reported: **MEAN (Standard Deviation)** for the number of subjects (N) as indicated. SLOPE is the slope of the least squares fit of the data points between the 8- and 30-minute samples (mg glucose.100 ml^{-1}.$minute^{-1}$ and μU insulin·ml^{-1}.$minute^{-1}$). G/I RATIO is the Glucose TOTAL AREA (mg glucose·100 ml^{-1}·minutes) / Insulin TOTAL AREA (μU INS·ml^{-1}·minutes). See Table 2 for additional information.

Table 5. Responses of biochemical variables to the Glucose/Insulin Clamp measured during the Standard Diet (STD) and at the end of the 21-day adaptation to a low carbohydrate/high fat diet (LCD).

Variable	N	STD Period		LCD Period	
		BASELINE	CLAMP	BASELINE	CLAMP
FFA	10	0.45 (0.19)	0.16 (0.07)e	0.62 (0.16)a	0.17 (0.05)e
Lactate	10	0.88 (0.23)	1.09 (0.23)	0.74 (0.14)	0.88 (0.22)
GDR	10	1.98 (0.30)	8.24 (2.17)e	1.83 (0.13)	8.21 (2.28)e
LOX	6	0.81 (0.33)	0.10 (0.25)e	1.14 (0.28)	0.82 (0.38)a
GOX	6	1.39 (0.63)	3.33 (0.79)e	0.45 (0.71)a	1.48 (0.79)ae
GNOX	6	0.60 (0.79)	4.44 (2.39)e	1.44 (0.76)	6.95 (2.29)ae
[INS]	10	7 (4)	76 (11)e	1 (1.5)a	67 (5)e
MUSC. Glyg.	8	49.3 (14.2)	69.4 (25.4)e	41.7 (15.0)	44.1 (11.9)
Muscle Enzymes:					
PDH	10				
Total		3.00 (1.99)	4.99 (3.04)	0.50 (1.51)a	0.37 (0.47)a
% Active		21.8 (28.1)	13.5 (7.0)	0.08 (0.25)a	4.4 (12.6)a
GS	10				
$FV_{0.1}$		0.08 (0.09)	0.28 (0.13)	0.12 (0.13)	0.45 (0.13)ae
%I		1.00 (0.63)	2.30 (1.58)	1.90 (1.90)	4.60 (2.52)ae
$A_{0.5}$		0.71 (0.38)	0.33 (0.25)	0.44 (0.25)	0.09 (0.09)ae

Values reported: MEAN (Standard Deviation) for the number of subjects (N) as indicated. Free Fatty Acids (FFA) (); Lactate ($mg \cdot dl^{-1}$); Glucose Disposal Rate (GDR) ($mg \cdot Kg^{-1} \cdot min^{-1}$); Insulin concentration ([INS]) ($\mu U \cdot ml^{-1}$); Lipid oxidation (LOX) ($mg \cdot Kg^{-1} \cdot min^{-1}$); Glucose oxidation (GOX) ($mg \cdot Kg^{-1} \cdot min^{-1}$); Non-Oxidative Glucose disposal (GNOX) ($mg \cdot Kg^{-1} \cdot min^{-1}$); Muscle Glycogen (MUSC. Glyg.) ($\mu mole \cdot gm^{-1}$ wet weight muscle); Pyruvate Dehydrogenase (PDH) (nM glucose·mg tissue $extract^{-1} \cdot min^{-1}$); Glycogen Synthetase (GS) (nM glucose·mg tissue $extract^{-1} \cdot min^{-1}$); Fractional Velocity ($FV_{0.1}$); Percent of GS activity independent of G-6-P stimulation (%I); Half maximal activity ($A_{0.5}$). Differences noted are $p < .05$: a = LCD Different from STD for same condition (BASELINE or CLAMP); e = CLAMP different from BASELINE for same period (STD or LCD).

increased non-oxidative glucose disposal (storage) during the insulin stimulated phase of the CLAMP, which correlated with a significant increase in glycogen synthetase (GS) activity. Accompanying these changes in enzyme activities, there was an average decline (n.s.) in resting muscle glycogen from 49.3 (μmole·gm^{-1}wet weight muscle) during the STD period to 41.7 or a difference of 8.3 ($\pm$ 42.6) by the end of the LCD period. Of interest, was a significant increase in muscle glycogen at the end of the three-hour CLAMP procedure during the STD period which did not occur during the LCD period.

The results of the Food Questionnaire are presented in Table 6. In general, there were very few and minor differences in overall food ratings between the Standard Diet and LCD periods. There were very few statistically significant patterns of change in responses to the questionnaire. During the LCD 7-11 and 17-21 period, there were fewer items for breakfast which the subjects "particularly liked." There was a decrease in the "appearance" rating of the lunch meal for the LCD 7-11 period. The subjects were more likely to indicate that they "did not get enough to eat" for the dinner meal during the first two days on the LCD (LCD 1-2), but there were fewer items which the individuals "did not like" and fewer "problems" during the same time period than noted for the STD. There were several comments worthwhile reporting. The general responses to both the STD Diet and the LCD were similar and favorable, with mean scores slightly above average for all of the periods. Several individuals reported dislike for selected food items [i.e., Polish sausage (2/10), cream cheese (2/10), salami (4/10), cheddar cheese (3/10), olives (1/10), and butter on crackers and sandwiches (2/10)]. There were an equal number of items which the subjects "liked better than average." These individual food preferences (or dislikes) were seemingly accentuated by a lack of a variety and being able to select meal food items (the menus were fixed), repetition of the menus (7-day rotation), and eating on a schedule. A few subjects indicated a preference for snacks between smaller meals, particularly during the STD due to the larger volume of food to be consumed at a meal. Other comments were related to preparation of the food and requests for more spices (food was too bland). Several of the subjects felt deprived from the limited caffeine intake during the entire study period.

Table 6. Summary of the responses to the 'Food Questionnaire' (Appendix B) during the Standard Diet (STD) and during three time periods of the 21-day adaptation to a low carbohydrate/high fat diet (LCD).

Question #	STD Period	LCD Period		
		Days 1-2	Days 7-11	Days 17-21
BREAKFAST:				
2	2.1 (0.6)	2.1 (0.6)	2.2 (0.6)	2.3 (0.6)
3	0.9 (0.4)	1.0 (0.0)	0.7 (0.4)	0.8 (0.4)
4	4.8 (0.9)	5.2 (0.8)	4.9 (1.0)	4.6 (0.5)
5	4.7 (0.9)	5.0 (0.7)	4.8 (1.0)	4.6 (0.5)
6	0.4 (0.4)	0.5 (0.5)	0.1 (0.2)a	0.1 (0.2)a
7	0.1 (0.2)	0.0 (0.0)	0.1 (0.2)	0.0 (0.1)
8	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
9	0.1 (0.2)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)
LUNCH:				
2	2.0 (0.6)	1.9 (0.6)	1.9 (0.5)	1.9 (0.6)
3	1.0 (0.6)	1.2 (0.4)	1.1 (0.4)	1.1 (0.5)
4	4.6 (1.0)	4.3 (0.8)	4.2 (0.7)	4.2 (0.5)
5	4.5 (0.8)	4.2 (1.3)	4.4 (0.8)	4.2 (0.7)
6	0.2 (0.3)	0.4 (0.5)	0.3 (0.4)	0.3 (0.3)
7	0.3 (0.4)	0.4 (0.5)	0.2 (0.3)	0.2 (0.2)
8	0.0 (0.0)	0.4 (0.8)	0.1 (0.3)	0.0 (0.0)
9	0.2 (0.2)	0.2 (0.4)	0.0 (0.1)	0.1 (0.1)
DINNER				
2	2.0 (0.7)	2.1 (0.7)	2.1 (0.8)	2.0 (0.8)
3	1.3 (0.4)	0.8 (0.4)a	0.8 (0.6)	0.9 (0.5)
4	4.5 (1.1)	4.4 (1.0)	4.5 (0.8)	4.8 (0.8)
5	4.4 (1.0)	4.6 (0.8)	4.7 (0.9)	4.8 (0.9)
6	0.4 (0.4)	0.4 (0.5)	0.5 (0.6)	0.3 (0.3)
7	0.2 (0.2)	0.0 (0.0)a	0.1 (0.2)	0.1 (0.1)
8	0.2 (0.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
9	0.2 (0.2)	0.0 (0.0)a	0.1 (0.2)	0.2 (0.3)

Values are **MEAN** (Standard Deviation) of the responses to the questionnaire completed during the STD period and the LCD period for Days 1-2, Days 7-11, and Days 17-21. Individual values used for each subject represent the mean of three questionnaires completed during the respective periods, except for LCD Days 1-2, which represent the scores for only one questionnaire. The values reported herein represent the mean of the individual subject's mean scores for each time period. Differences noted ('a') indicate LCD Different from STD for same question ($p < .05$).

The results of the "Daily Diary" Questionnaire are reported in Tables 7 and 8. In Table 7, the average frequency of responses to the questions (outlined in Appendix C) are listed. Compared to the STD period, there were more days for which a comment of "NO Problems" was made during the LCD 17-22 day pericd. During some LCD periods, there were also fewer: "headaches;" reports of "dizziness;" "gas pressure" complaints; episodes of "feeling sick to my stomach;" reports of decreased "concentration;" and complaints of "dry mouth." Table 8 listed the average severity of those symptoms reported. During the LCD 1-5 and 6-10 day periods, the reported severity of "heart beating fast" was greater, while "dizziness," "sick to my stomach," "gas pressure," "loss of concentration," "dry mouth," and "difficulty sleeping" were less severe during LCD periods than during the STD period. Individual comments listed were generally scanty and related to outside activities. However, there were several comments which reoccurred. Many of the subjects had variable difficulties sleeping in the hospital due to strange surroundings, noises, and disturbances by nursing personnel. The disturbed sleep may have affected how they felt, and their performance on the PAB during the subsequent day. Several had unusual dreams of vivid quality, which frequently related to food. Most subjects had several irregularly interspersed days on the LCD during which time they felt unusually energetic. Many had reported muscle soreness related to intense physical activities unrelated to the demands of the study. Four of the subjects were competitive athletes, and reported unusual muscle burning during intense training activities. The muscle discomfort was greatest during days 4-14 on the LCD, but it did not prohibit any physical activities (even strenuous training), and seemed to improve considerably near the end of the 22-day LCD period.

DISCUSSION

The low carbohydrate/high fat diet (LCD) was very well-tolerated, with minimal physical and psychological difficulties, and evidenced significant metabolic adaptations to chronic consumption of the LCD. [One of the most interesting findings was a 30% decrease in fasting blood triglycerides and a corresponding 20% increase in HDL-cholesterol. Total cholesterol was not significantly changed in face of a more than two-fold increase in cholesterol and fat intake.] The response to an intravenous glucose challenge (IV-GTT)

Table 7. Summary of Average Frequency of symptoms reported on the 'Daily Diary' questionnaire (Appendix C) during the Standard Diet (STD) and during four time periods of the 21-day adaptation to a low carbohydrate/high fat diet (LCD).

Question #	STD Period	LCD Period			
		L 1-5	L 6-10	L 11-16	L 17-22
0	1.8 (1.8)	2.2 (1.5)	1.5 (1.7)	2.6 (1.7)	3.3 (2.6)k
1	1.1 (1.0)	0.4 (0.7)a	1.2 (1.3)	1.3 (2.0)	0.7 (1.1)
2	0.6 (1.1)	0.6 (1.1)	0.8 (1.5)	0.2 (0.4)	0.4 (1.0)
3	0.3 (0.5)	0.2 (0.6)	0.3 (0.5)	0.0 (0.0)a	0.4 (0.7)
4	0.2 (0.4)	0.1 (0.3)	0.2 (0.4)	0.2 (0.6)	0.0 (0.0)
5	0.3 (0.5)	0.1 (0.3)	0.2 (0.4)	0.1 (0.3)	0.3 (0.7)
6	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)k	0.2 (0.6)	0.0 (0.0)
7	0.1 (0.3)	0.4 (1.0)	0.6 (0.8)	0.4 (1.3)	0.1 (0.3)
8	0.2 (0.4)	0.4 (1.0)	0.3 (0.7)	0.2 (0.4)	0.1 (0.3)
9	1.1 (1.3)	0.7 (1.5)	0.8 (1.3)	1.0 (1.5)	0.8 (1.0)
10	1.0 (1.3)	0.6 (1.1)	1.4 (1.7)	1.8 (1.7)	1.3 (2.2)
11	1.9 (1.9)	1.5 (1.5)	1.3 (1.3)	1.3 (1.6)	1.2 (1.8)
12	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.1 (0.3)	0.1 (0.3)
13	0.5 (0.9)	0.4 (0.7)	0.6 (0.8)	1.0 (1.3)	1.1 (1.5)
14	0.6 (0.8)	0.3 (1.0)	0.3 (0.5)	0.4 (0.8)	0.0 (0.0)a
15	1.5 (1.6)	0.0 (0.0)a	0.2 (0.6)	0.0 (0.0)a	0.2 (0.6)
16	0.2 (0.4)	0.4 (0.7)	0.1 (0.3)	0.2 (0.4)	0.4 (0.7)
17	0.7 (0.8)	0.2 (0.4)	0.4 (0.5)	0.3 (0.5)	0.3 (0.7)
18	0.2 (0.4)	0.1 (0.3)	0.1 (0.3)	0.2 (0.4)	0.1 (0.3)
19	0.3 (0.7)	0.5 (1.1)	0.5 (1.0)	0.2 (0.6)	0.2 (0.4)
20	0.3 (0.7)	0.2 (0.4)	0.0 (0.0)	0.4 (1.3)	0.3 (0.7)
21	0.1 (0.3)	0.0 (0.0)	0.4 (0.7)	0.5 (1.1)	0.3 (0.5)
22	0.3 (0.7)	0.3 (0.7)	0.8 (1.3)	0.4 (0.7)	0.9 (1.4)
23	0.5 (1.0)	0.6 (1.1)	0.4 (0.7)	0.5 (1.3)	0.5 (0.7)
24	0.6 (0.7)	0.5 (0.7)	0.3 (0.7)k	0.1 (0.3)a	0.8 (1.6)
25	0.9 (1.7)	0.1 (0.3)	0.2 (0.2)	0.2 (0.6)	0.4 (0.7)
26	0.3 (0.7)	0.0 (0.0)	0.1 (0.3)	0.0 (0.0)	0.0 (0.0)
27	0.6 (1.0)	0.2 (0.6)	0.0 (0.0)a	0.5 (1.3)	0.3 (0.7)
28	0.1 (0.3)	0.1 (0.3)	0.2 (0.4)	0.1 (0.3)	0.3 (0.7)
29	1.0 (0.9)	0.9 (1.0)	1.6 (1.6)	1.8 (1.9)	1.6 (1.6)
30	0.3 (0.5)	0.3 (0.7)	0.3 (1.0)	0.1 (0.3)	0.0 (0.0)
31	0.2 (0.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
32	0.2 (0.4)	0.4 (0.8)	0.1 (0.3)	0.2 (0.4)	0.0 (0.0)

Values are MEAN (Standard Deviation) of the responses to the questionnaire completed daily during the STD period and during the LCD period for Days 1-5 (L 1-5), Days 6-10 (L 6-10), Days 11-16 (L 11-16), and Days 17-22 (L 17-22). Individual values used for each subject represent the mean of all questionnaires completed during the respective periods. The values reported herein represent the mean of the individual subject's mean scores for each time period. Differences noted indicate LCD Different from STD for same question with 'a' signifying $p < .05$ and 'k' signifying $p < .10$.

Table 8. Summary of Average Severity of symptoms reported on the 'Daily Diary' questionnaire (Appendix C) during the Standard Diet (STD) and during four time periods of the 21-day adaptation to a low carbohydrate/high fat diet (LCD).

Question #	STD Period	LCD Period			
		L 1-5	L 6-10	L 11-16	L 17-22
0	—	—	—	—	—
1	0.9 (0.7)	0.5 (1.0)	0.6 (0.7)	0.9 (1.3)	0.6 (0.9)
2	0.4 (0.7)	0.4 (0.7)	0.2 (0.4)	0.2 (0.5)	0.1 (0.3)
3	0.4 (0.7)	0.1 (0.4)	0.3 (0.5)	0.0 (0.0)a	0.5 (0.9)
4	0.3 (0.5)	0.4 (1.3)	0.2 (0.5)	0.1 (0.4)	0.0 (0.0)
5	0.4 (0.7)	0.1 (0.2)	0.4 (0.8)	0.2 (0.6)	0.7 (1.9)
6	0.1 (0.2)	0.6 (1.9)	0.2 (0.5)	0.3 (0.8)	0.0 (0.0)
7	0.1 (0.2)	0.6 (1.5)k	0.6 (1.0)a	0.3 (1.0)	0.6 (1.9)
8	0.2 (0.4)	0.2 (0.4)	0.5 (1.3)	0.2 (0.4)	0.2 (0.6)
9	0.5 (0.6)	0.3 (0.7)	1.3 (2.0)	0.9 (1.2)	1.5 (2.1)
10	0.4 (0.6)	1.2 (1.9)	1.5 (2.0)	1.5 (1.7)	1.4 (1.8)
11	0.8 (0.8)	1.3 (1.3)	1.1 (1.3)	0.7 (0.7)	1.5 (2.1)
12	0.5 (1.3)	1.2 (0.4)	0.4 (0.8)	0.6 (1.9)	0.2 (0.6)
13	0.5 (1.0)	0.3 (0.5)	0.6 (1.2)	1.6 (2.0)	1.2 (1.7)
14	0.5 (0.8)	0.2 (0.6)	0.8 (1.9)	0.5 (1.4)	0.0 (0.0)a
15	1.1 (1.3)	0.0 (0.0)a	0.1 (0.2)a	0.0 (0.0)a	0.1 (0.2)a
16	0.2 (0.3)	0.5 (0.9)	0.2 (0.6)	0.3 (0.7)	0.5 (1.3)
17	0.6 (0.7)	0.2 (0.3)	0.8 (1.9)	0.9 (1.7)	0.4 (0.8)
18	0.3 (0.5)	0.1 (0.3)	0.1 (0.2)	0.7 (1.9)	0.1 (0.2)
19	0.3 (0.7)	1.1 (2.4)	1.6 (2.6)	0.4 (1.1)	0.5 (1.3)
20	0.3 (0.7)	0.8 (1.7)	0.0 (0.0)	0.1 (0.3)	0.3 (0.7)
21	0.4 (1.3)	0.0 (0.0)	1.0 (1.9)	0.7 (1.5)	1.4 (2.3)
22	0.3 (0.7)	0.5 (1.3)	0.6 (1.2)	0.6 (1.1)	1.1 (1.7)
23	0.3 (0.6)	0.5 (0.9)	0.6 (1.3)	0.2 (0.5)	0.5 (0.8)
24	0.5 (0.7)	0.5 (0.7)	0.6 (1.4)	0.1 (0.3)a	0.6 (1.2)
25	0.3 (0.6)	0.2 (0.6)	0.1 (0.2)	0.4 (1.2)	0.2 (0.4)
26	0.2 (0.5)	0.0 (0.0)	0.6 (1.9)	0.0 (0.0)	0.0 (0.0)
27	0.2 (0.4)	0.2 (0.7)	0.0 (0.0)k	0.2 (0.5)	0.2 (0.4)
28	0.2 (0.6)	0.1 (0.3)	0.4 (0.8)	0.2 (0.5)	0.2 (0.5)
29	1.3 (1.4)	1.7 (1.8)	2.2 (2.1)	1.9 (1.9)	2.0 (1.8)
30	0.9 (1.9)	0.7 (1.6)	0.4 (1.2)k	0.6 (1.9)	0.0 (0.0)
31	0.2 (0.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
32	0.3 (0.6)	0.2 (0.4)	0.1 (0.3)	0.3 (0.7)	0.0 (0.0)

Values are MEAN (Standard Deviation). See Table 7 for legend.

was markedly altered, but there was no consistent alteration in insulin sensitivity. There was a hormone response pattern similar to that seen in starvation (5,21), hypocaloric weight loss diets (4, 29) and carbohydrate deprivation (12, 27, 28). Our subjects exhibited a similar decline in thyroid hormone accompanied by a transient rise in cortisol even though they were fed a eucaloric diet. [A transient decline in blood glucose and slight increase in blood ketone bodies observed in the current study was similar to the previous study on swine study (12). Other studies using more severe carbohydrate restriction from either starvation, modified fasting, or a eucaloric 1% carbohydrate diet produced sustained declines in blood glucose and pronounced elevations in blood ketone bodies (4, 5, 20, 21, 27, 28, 29).] Rats appear to manifest responses to carbohydrate deprivation or starvation (20, 30, 34) different from those observed in man. The rats showed no depression of resting blood glucose concentration with either 1% or 5.7% carbohydrate diets (20, 30). Furthermore, 24-hour starvation improved exercise endurance in rats (8) whereas reductions in endurance were observed in man (19, 23).

The meal response tests demonstrated the stimulus for the metabolic adaptations, and revealed some striking comparisons. The integrated responses over nine hours of the day covering two meals showed that both the insulin and triglyceride areas were markedly less during the LCD than that measured during the Standard Diet (STD) period. These responses are highly suggestive that carbohydrate may play a significant role in the development of postprandial hypertriglyceridemia. These dynamic tests (Meal and Breakfast Response Tests) further indicated that standard fasting measures of blood triglycerides may not be indicative of the true status of many individuals with certain metabolic problems.

GENERAL RESPONSES TO THE LCD. Many of the responses to both the "Daily Diary" and "Food Questionnaire" were undoubtedly tainted by the confinement to the hospital environment. The probable acclimation to the hospital environment and impending completion of the study are possible reasons why many of the problems noted during the STD period were less during all or part of the LCD period. However, it is important to note that the potential complaints which we had anticipated during the LCD adaptation period did not

occur. All of the subjects were able to carry on with their normal daily activities without substantial compromise. These activities included college exams, normal work routines, and intense physical activities. The physical symptoms were generally mild and transient, while the psychological symptoms were very minor and provided no evidence of impaired function on the preliminary evaluation of the PAB scores. There were no complaints of any gastrointestinal distress which could be attributed to the LCD.

EFFECTS ON CONTROL OF GLUCOSE METABOLISM. Insulin has been shown to play a critical role in the control of intermediary metabolism. Variations in insulin sensitivity occur by alterations in insulin binding to cell membranes and intracellular actions on metabolic enzyme activities. Significant intracellular rate-limiting enzymes controlled by insulin are pyruvate dehydrogenase (PDH) (glucose oxidation) and glycogen synthetase (GS) (glycogen storage). The results from our previous study in swine which were adapted to the LCD, demonstrated a change in the pattern of response to the suddenly elevated blood glucose concentrations experienced during a glucose tolerance test (GTT) (12). In the current study, a similar reduction in the insulin response to the intravenous glucose tolerance test (IV-GTT) was observed as reflected by the 2-fold increase in the Glucose area/Insulin area ratios (Table 4). A reasonable interpretation of this alteration in the glucose/insulin ratio is a decrease in insulin sensitivity. The two factors which comprise this difference are: 1) an apparent failure of the pancreatic beta cells to release more insulin in face of glucose concentrations above those measured during the STD period; and 2) an indication of a difference in insulin sensitivity. However, the glucose/insulin clamps (CLAMP) data did not demonstrate any alterations in insulin sensitivity. A study in rats maintained on a 10% carbohydrate/68% fat diet for 30 days demonstrated a decrease in insulin sensitivity (32), while another study utilizing an 11.7% carbohydrate diet in rats demonstrated a decline in insulin binding (13). However, carbohydrate deprivation in rats produced an elevation (13) or no change (32) in resting insulin concentration in contrast to man (4, 27, 28, 29) and pigs (12) whose resting insulin declined. These differences in response to carbohydrate deprivation between man and rats, as well as the potential discrepancy between our two measures of insulin sensitivity (IV-GTT vs. CLAMP), open further questions regarding the mechanisms of the altered

metabolic response pattern and the validity of the rat as an appropriate model. Knowledge of the mechanisms regulating glucose metabolism is an important factor in understanding the utility of comprehensive dietary regimens.

EFFECTS ON FAT METABOLISM AND LIPIDS. The 30% decline in blood triglycerides is similar to reports in previous studies utilizing low carbohydrate/high fat diets ranging from 1% to 19% carbohydrate (1, 10, 12, 27, 28, 34). The total cholesterol was unchanged in the current study and for a previous 19% carbohydrate diet (34), but was increased from the 1% carbohydrate/85% fat diet (27, 28). We also measured an increase in high density lipoprotein (HDL) cholesterol similar to that reported in the 19% carbohydrate diet. The increase in total cholesterol in the reports by Phinney et al. (27, 28) may have been related to the substantial intake of cholesterol, although intake was only slightly greater than ours. The mechanism for the increase in HDL cholesterol is uncertain, but it is likely to be related to the increased fat transport required to support the increases in lipid metabolism observed in the current data and previous reports. The reductions in blood triglycerides are a result of decreased endogenous production of triglycerides in the liver coupled with increased utilization. This alteration in triglyceride kinetics is indicated by the markedly lower Adjusted Triglyceride Area for the Meal Response Test (MRT) during the LCD period as compared to the STD period. Our data indicated these modifications in glucose and lipid metabolism were accompanied by a 30% increase in circulating free fatty acids (FFAs) and a transient (70%) increase in ß-OH-butyrate. Previous studies in man have reported increases in FFAs of 34-100% for either starvation or carbohydrate deprivation (5, 28, 29). A similar increase was reported in pigs (12), but was not elevated in rats on a 5.7% carbohydrate diet (30). The increase in FFAs is reflective of an increase in lipoprotein lipase activity (34). During the LCD, our subjects were consistently ketotic, as reflected by elevated urine ketone concentrations. However, the modest elevation in blood ß-OH-butyrate, similar to that observed in the pigs (12), was substantially less than the 30-100 fold elevations previously reported from more severe carbohydrate restriction in man (4, 5, 28, 29). Once again, the data obtained from rats on similar composition diets differed from man by showing lower elevations of up to only an eight-fold increase (20, 30). The previous

work by Phinney et al. (27, 28, 29) dispelled the previously held belief that ketosis, per se, was harmful. Although the ketosis observed in our study was less pronounced, there were no indications of any deleterious effects. Higher carbohydrate content in the diet would prevent the elevations in blood ketones, but may negatively influence the metabolic adaptations to the LCD. The current and previous studies utilizing higher, but still deficient, carbohydrate diets, indicate that the beneficial metabolic adaptations to an LCD would occur (to some extent) with diets with up to 20% carbohydrate. However, there is probably an optimal composition which may vary dependent upon the specific metabolic effect desired.

POTENTIAL UTILITY FOR IMPROVING EXERCISE ENDURANCE. The increase in resting fat metabolism without a reduction in muscle glycogen after adaptation to the LCD agrees with our previous swine data (12), and confirms the potential use of an LCD regime as a means of increasing moderate intensity endurance exercise. The LCD-adapted pigs exhibited a 30% increase in moderate intensity endurance (65% $\dot{V}O_2$ Max). All of the previous studies utilizing lower carbohydrate content diets have produced reductions in muscle glycogen (20, 27, 29). A study utilizing severe caloric restriction (830 calories/day) preserved muscle glycogen by supplying 300 calories/day as carbohydrate (4). This amount of carbohydrate is comparable to that supplied in the current and the previous pig (12) studies. The preservation of muscle glycogen thus appears to be related to the prevention of severe ketosis. Although an increase in endurance has been demonstrated in swine, the real effects and practical utility in man remains to be evaluated. The strong metabolic similarities between man and swine as noted above are very suggestive that the 7% (or slightly higher) carbohydrate diet could produce similar advantages for increasing moderate (or lower) intensity exercise endurance. The positive response to the LCD meals indicates that with modifications to increase flavor (seasoning) and selections of LCD foods, the LCD would not be difficult to maintain for motivated individuals.

CONCLUSION

Beneficial effects on metabolism have been produced by a three-week adaptation to the low carbohydrate/high fat diet (LCD). These include reduced blood triglycerides, increased HDL-cholesterol, unchanged blood glucose and muscle glycogen, and no substantial difficulties from consuming the diet. [The alterations in metabolism may be potentially useful in treatment of some severe metabolic disorders affecting both fat and glucose utilization.] These clinical applications warrant further investigation. The discussion has partially elucidated many metabolic similarities between man and swine, while substantial differences appear to exist between man and rats. More detailed discussions of these and other data not included in this report will be presented in subsequent publications.

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APPENDICES

Appendix A: Overall Individual Schedule for study.

Appendix B: Food Questionnaire

Appendix C: Daily Diary

Appendix D: Sample Diets

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE I: (Suitability Evaluation) **Completed**

1. Explanation of study (general) **Date:**__/__/__ ____
2. General questionnaire [Health, Diet, Exercise (EX)] ____
3. If qualified, Informed Consent ____
4. Complete History & Physical Exam (M.D.) ____
5. Morning Urine and Blood Samples ____
6. Initial Screening: ____PASS ___FAIL ____

PHASE II: [Initial Measurements & Outpatient Standard Diet (STD) period]]

			DAY
		Date:__/__/__(M)	
I.	Introduction to Performance Assessment Battery (PAB)#1	____	(S-1)
II.	Intralipid test dose	____	(S-1)
III.	Instruction in maintaining exercise (EX) Record	____	(S-1)
IV.	Instruction for Diet Record (4 days)	____	(S-1)
V.	Body Weight (WT)	____	(S-1)
IV.	Instruction to abstain from alcohol consumption	____	(S-1)
VI.	S-Max Energy Efficiency (Eff.) Cycle EX (Training)	____	(S-1)
V.	Body Weight (at Home) **Date:**__/__/__(W)	____	(S-2)
I.	PAB (#2)	____	(S-2)
VI.	S-Max Energy Eff. Cycle EX (Training)	____	(S-2)
IV.	Begin Diet Record	____	(S-2)
III.	Check EX Record	____	(S-2)
V.	Body Weight (at Home) **Date:**__/__/__(F)	____	(S-3)
I.	PAB (#3)	____	(S-3)
VI.	S-Max Energy Eff. Cycle EX (Training)	____	(S-3)
IV.	Check progress on Diet Record	____	(S-3)
III.	Check EX Record	____	(S-3)
III.	Check EX Record **Date:**__/__/__(M)	____	(S-4)
IV.	Check COMPLETED Diet Record	____	(S-4)
0.	Fill in DATES on the remainder of the protocol	____	(S-4)

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE II: [Initial Measurements & Outpatient Standard Diet (STD) Period]

				DAY
V.	Body Weight (at Home)	Date:___/___/___(W)	____	(S-5)
I.	PAB (#4)		____	(S-5)
VI.	S-Max Energy Eff. Cycle EX (Training)		____	(S-5)
III.	Check EX Record		____	(S-5)
IV.	Instructions to continue to abstain from alcohol		____	(S-5)
IV.	Instructions to limit daily Caffeine intake (300 mg)		____	(S-5)
IV.	Given Standard Diet, Grocery list, & Check List		____	(S-5)
$$.	Grocery allotment ($50)		____	(S-5)
V.	Body Weight (at Home)	Date:___/___/___(F)	____	(S-6)
I.	PAB (#5)		____	(S-6)
IV.	Check progress on STD		____	(S-6)
III.	Check EX Record, Medical Check-up		____	(S-6)
VI.	S-Max Energy Eff. Cycle EX (Training)		____	(S-6)
IV.	Instructed to begin STD Diet (Daily WT; Check List)		____	(S-6)
0.	**BEGIN STD Diet (Day #1)**	Date:___/___/___(F)	____	(S-7)
V.	Check Daily WTs, Body WT (STD Day #4)	Date:___/___/___(Sa)	____	(S-8)
IV.	Food Check List		____	(S-8)
III.	Check EX Record, Medical Check-up		____	(S-8)
IV.	Adjust Diet (if needed)		____	(S-8)

PHASE III: [Standard Diet (STD) Hospital Testing Period]

				Hospital Days
0.	STD Day #6	Date:___/___/___(Th)	____	(H-0)
X.	Cycle Ergometer Max test #1		____	(H-0)
IV.	Food Check List		____	(H-0)
IV.	Adjust Diet (if needed)		____	(H-0)
0.	**ADMIT to UCSD Clinical Research Center (CRC)**		____	(H-0)
0.	STD Day #7	Date:___/___/___(F)	____	(H-1)
XII.	Breakfast Response Test (BRT)		____	(H-1)
V.	Body Weight #1		____	(H-1)
	{OVERNIGHT PASS, if desired}			

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE III: [Standard Diet (STD) Hospital Testing Period]

			Hospital Days
0.	STD Day #8	Date:__/__/__(Sa) ____	(H-1a)
	{Free for the day (take lunch); return for dinner}		
	{OVERNIGHT PASS, if desired}		
0.	STD Day #9	Date:__/__/__(Su) ____	(H-2)
V.	Body Weight #2	____	(H-2)
	{Free for the day (take lunch); return for dinner}		
0.	STD Day #10	Date:__/__/__(M) ____	(H-3)
V.	Body Weight #3, Urine Specific Gravity (SG) #3	____	(H-3)
VI.	S-Max Energy Eff. Cycle EX (#1)	____	(H-3)
I.	PAB (#6)	____	(H-3)
III.	Check EX Record, Medical Check-up	____	(H-3)
XI.	Begin 24-Hr Urine collection (#1)	____	(H-3)
XI.	Begin 3-day Stool collection (#1)	____	(H-3)
XI.	Composite Food Sample: STD Diet (by Dietician) (#1)	____	(H-3)
IV.	Food Questionnaire #1	____	(H-3)
0.	STD Day #11	Date:__/__/__(Tu) ____	(H-4)
V.	Body Weight #4, Urine SG #4	____	(H-4)
II.	IV Fat Tolerance Test (IV-FTT)(#1)	____	(H-4)
I.	PAB (#7)	____	(H-4)
XI.	Complete 24-Hr Urine collection (#1)	____	(H-4)
XI.	Continue 3-day Stool collection (#1)	____	(H-4)
XI.	Composite Food Sample: STD Diet (by Dietician) (#2)	____	(H-4)
IV.	Food Questionnaire #2	____	(H-4)
	{Free for the afternoon (take lunch); return for dinner}		

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE III: [Standard Diet (STD) Hospital Testing Period]

			Hospital Days
0.	STD Day #12	Date:__/__/__(W) ____	(H-5)
V.	Body Weight #5, Urine SG #5	____	(H-5)
VII.	Morning Blood Sample [with Meal Response Test (MRT)]	____	(H-5)
XII.	MRT (#1)	____	(H-5)
I.	PAB (#8)	____	(H-5)
XI.	Complete 24-Hr Urine collection (#2)	____	(H-5)
XI.	Begin 24-Hr Urine collection (#3)	____	(H-5)
XI.	Continue 3-day Stool collection (#1)	____	(H-5)
XI.	Composite Food Sample: STD (by Dietician) (#3)	____	(H-5)
IV.	Food Questionnaire #3	____	(H-5)
	{Free for afternoon (take lunch); return for dinner}		
0.	STD Day #13	Date:__/__/__(Th) ____	(H-6)
III.	Check EX Record, Medical Check-up	____	(H-6)
VII.	Morning Blood Sample [with Glucose Tolerance Test (GTT)]	____	(H-6)
XX.	IV-GTT (#1)	____	(H-6)
XI.	Complete 24-Hr Urine collection (#3)	____	(H-6)
XI.	Complete 3-day Stool collection (#1)	____	(H-6)
	{Free for afternoon (take lunch); return for dinner}		
0.	STD Day #14	Date:__/__/__(F) ____	(H-7)
V.	Body Weight #6, Urine SG #6	____	(H-7)
XXI.	Glucose Clamp (CLAMP)/Muscle Biopsy (#1)	____	(H-7)
0.	Last day of STD	____	(H-7)
	{Release Until Beginning of PHASE IV; FREE Diet}		

PHASE IV: [Low Carbohydrate/High Fat Diet (LCD) Hospital Period]

0.	LCD Day #1	Date:__/__/__(M) ____	(H-8)
0.	Report to CRC early am for Re-admission; BEGIN LCD	____	(H-8)
III.	Check EX Record, Medical Check-up	____	(H-8)
	{Free for day (take lunch); return for dinner}		

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE IV: [Low Carbohydrate/High Fat Diet (LCD) Hospital period]

			Hospital Days
0.	LCD Day #2	Date:__/__/__(Tu) ____	(H-9)
V.	Body Weight #7, Urine SG #7	____	(H-9)
VII.	Morning Blood Sample	____	(H-9)
I.	PAB (#9)	____	(H-9)
IV.	Food Questionnaire #4	____	(H-9)
	{Free for day (take lunch); return for dinner}		
	{OVERNIGHT PASS, if desired}		
0.	LCD Day #3	Date:__/__/__(W) ____	(H-10)
0.	NO Testing	____	(H-10)
	{Free for day (take lunch); return for dinner}		
0.	LCD Day #4	Date:__/__/__(Th)____	(H-11)
V.	Body Weight #8, Urine SG #8	____	(H-11)
VII.	Morning Blood Sample	____	(H-11)
I.	PAB (#10)	____	(H-11)
VI.	S-Max Energy Eff. Cycle EX (#2)	____	(H-11)
III.	Check EX Record, Medical Check-up	____	(H-11)
	{Free for day (take lunch); return for dinner}		
	{OVERNIGHT PASS, if desired}		
0.	(LCD Day #5)	Date:__/__/__(F) ____	(H-12)
V.	Body Weight #9	____	(H-12)
X.	Cycle Ergometer Max test #2	____	(H-12)
	{Free for day (take lunch); return for dinner}		
	{OVERNIGHT PASS, if desired}		
0.	LCD Day #6	Date:__/__/__(Sa)____	(H-13)
0.	NO TESTING	____	(H-13)
	{Free for day (take lunch); return for dinner}		
	{OVERNIGHT PASS, if desired}		
0.	LCD Day #7	Date:__/__/__(Su)____	(H-14)
0.	NO TESTING	____	(H-14)
	{Free for day (take lunch); return for dinner}		

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE IV: (Low Carbohydrate/High Fat Diet (LCD) Hospital period)

			Hospital Days
0.	LCD Day #8	Date:___/___/___(M) ____	(H-15)
V.	Body Weight #10, Urine SG #10	____	(H-15)
VII.	Morning Blood Sample (with MRT)	____	(H-15)
XII.	MRT (#2)	____	(H-15)
III.	Check EX Record, Medical Check-up	____	(H-15)
XI.	Begin 24-Hr Urine collection (#4)	____	(H-15)
XI.	Begin 3-day Stool collection (#2)	____	(H-15)
XI.	Composite Food Sample: STD Diet (by Dietician) (#4)	____	(H-15)
IV.	Food Questionnaire #5	____	(H-15)
0.	LCD Day #9	Date:___/___/___(Tu)____	(H-16)
V.	Body Weight #11, Urine SG #11	____	(H-16)
II.	IV Fat Tolerance Test (#2)	____	(H-16)
I.	PAB (#11)	____	(H-16)
XI.	Complete 24-Hr Urine collection (#4)	____	(H-16)
XI.	Begin 24-Hr Urine collection (#5)	____	(H-16)
XI.	Continue 3-day Stool collection (#2)	____	(H-16)
XI.	Composite Food Sample: STD (by Dietician) (#5)	____	(H-16)
IV.	Food Questionnaire #5	____	(H-16)
	{Free for afternoon (take lunch); return for dinner}		
0.	LCD Day #10	Date:___/___/___(W)____	(H-17)
V.	Body Weight #12, Urine SG #12	____	(H-17)
VII.	Morning Blood Sample (with GTT)	____	(H-17)
XX.	IV-GTT(#2)	____	(H-17)
I.	PAB (#12)	____	(H-17)
XI.	Complete 24-Hr Urine collection (#5)	____	(H-17)
XI.	Begin 24-Hr Urine collection (#6)	____	(H-17)
XI.	Continue 3-day Stool collection (#2)	____	(H-17)
XI.	Composite Food Sample: STD Diet (by Dietician) (#6)	____	(H-17)
IV.	Food Questionnaire #7	____	(H-17)
	{Free for afternoon (take lunch); return for dinner}		

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE IV: (Low Carbohydrate/High Fat Diet (LCD) Hospital period)

			Hospital Days	
0.	LCD Day #11	Date:__/__/__(Th)	____	(H-18)
V.	Body Weight #13, Urine SG #13		____	(H-18)
VI.	S-Max Energ-Hr Eff. Cycle EX (#3)		____	(H-18)
III.	Check EX Record, Medical Check-up		____	(H-18)
XI.	Complete 24-Hr Urine collection (#6)		____	(H-18)
XI.	Complete 3-day Stool collection (#2)		____	(H-18)
	{Free for afternoon (take lunch); return for dinner}			
	{OVERNIGHT PASS, if desired}			
0.	LCD Day #12	Date:__/__/__(F)	____	(H-19)
0.	NO TESTING		____	(H-19)
	{Free for day (take lunch); return for dinner}			
	{OVERNIGHT PASS, if desired}			
0.	LCD Day #13	Date:__/__/__(Sa)	____	(H-20)
0.	NO TESTING		____	(H-20)
	{Free for day (take lunch); return for dinner}			
	{OVERNIGHT PASS, if desired}			
0.	LCD Day #14	Date:__/__/__(Su)	____	(H-21)
0.	NO TESTING		____	(H-21)
	{Free for day (take lunch); return for dinner}			
	{OVERNIGHT PASS, if desired}			
0.	LCD Day #15	Date:__/__/__(M)	____	(H-22)
III.	Check EX Record, Medical Check-up		____	(H-22)
	{Free for day (take lunch); return for dinner}			
	{OVERNIGHT PASS, if desired}			
0.	LCD Day #16	Date:__/__/__(Tu)	____	(H-23)
V.	Body Weight #14		____	(H-23)
X.	Cycle Ergometer Max test #3		____	(H-23)
	{Free for afternoon (take lunch); return for dinner}			
	{OVERNIGHT PASS, if desired}			

Name: J. Doe (Subject # 11)

APPENDIX A

Overall Test Schedule

PHASE IV: (Low Carbohydrate/High Fat Diet (LCD) Hospital period)

			Hospital Days	
0.	LCD Day #17	Date:___/___/___(W)	____	(H-24)
XI.	Begin 24-Hr Urine collection (#7)		____	(H-24)
XI.	Begin 3-day Stool collection (#3)		____	(H-24)
VI.	S-Max Energy Eff. Cycle EX (#4)		____	(H-24)
XI.	Composite Food Sample: STD (by Dietician) (#7)		____	(H-24)
IV.	Food Questionnaire #8		____	(H-24)
	{Free for afternoon (take lunch); return for dinner}			
0.	LCD Day #18	Date:___/___/___(Th)	____	(H-25)
V.	Body Weight #15, Urine SG #15		____	(H-25)
VII.	Morning Blood Sample (with MRT)		____	(H-25)
XII.	MRT (#3)		____	(H-25)
III.	Check EX Record, Medical Check-up		____	(H-25)
XI.	Complete 24-Hr Urine collection (#7)		____	(H-25)
XI.	Begin 24-Hr Urine collection (#8)		____	(H-25)
XI.	Continue 3-day Stool collection (#3)		____	(H-25)
XI.	Composite Food Sample: STD (by Dietician) (#8)		____	(H-25)
IV.	Food Questionnaire #9		____	(H-25)
0.	LCD Day #19	Date:___/___/___(F)	____	(H-26)
V.	Body Weight #16, Urine SG #16		____	(H-26)
II.	IV Fat Tolerance Test (#3)		____	(H-26)
I.	PAB (#13)		____	(H-26)
XI.	Complete 24-Hr Urine collection (#8)		____	(H-26)
XI.	Begin 24-Hr Urine collection (#9)		____	(H-26)
XI.	Continue 3-day Stool collection (#3)		____	(H-26)
XI.	Composite Food Sample: STD (by Dietician) (#9)		____	(H-26)
IV.	Food Questionnaire #10		____	(H-26)
	{Free for afternoon (take lunch); return for dinner}			

Name: J. Doe (Subject # 11) **APPENDIX A**

Overall Test Schedule

PHASE IV: (Low Carbohydrate/High Fat Diet (LCD) Hospital period)

			Hospital Days
0.	LCD Day #20	Date:__/__/__(S)	____ (H-27)
XI.	Complete 24-Hr Urine collection (#9)		____ (H-27)
XI.	Complete 3-day Stool collection (#3)		____ (H-27)
	{Free for afternoon (take lunch); return for dinner}		
	{OVERNIGHT PASS, if desired}		
0.	LCD Day #21	Date:__/__/__(Su)	____ (H-28)
0.	NO TESTING		____ (H-28)
	{Free for day (take lunch); return for dinner}		
	{OVERNIGHT PASS, if desired}		
0.	LCD Day #22	Date:__/__/__(M)	____ (H-29)
0.	NO TESTING		____ (H-29)
	{Free for day (take lunch); return for dinner}		
0.	LCD Day #23	Date:__/__/__(Tu)	____ (H-30)
V.	Body Weight #17, Urine SG #17		____ (H-30)
VII.	Morning Blood Sample (with GTT)		____ (H-30)
XX.	IV Glucose Tolerance Test (#3)		____ (H-30)
III.	Check EX Record, Medical Check-up		____ (H-30)
0.	LCD Day #24	Date:__/__/__(W)	____ (H-31)
XXI.	Glucose Clamp/Muscle Biopsy (#2)		____ (H-31)

Name: J. Doe (Subject #11) **APPENDIX B**

FOOD QUESTIONNAIRE

BACKGROUND

You have been selected as a subject to evaluate the potential effectiveness of using a Low Carbohydrate/High Fat Diet (LCD) to temporarily change the metabolism of the body. The changes in metabolism may prove to be beneficial in increasing long-duration exercise endurance and/or as a means of treating certain diseases of metabolism.

The appreciation of food is very dependent on your personal taste preferences and on preconceived notions about taste. Certain foods may 'taste bad' to you just because you 'think' they should taste bad. (People have frequently been known to like a mystery food until they are told what it actually is.) Eating 'fatty' foods has a bad sound, in part due to the bad press which consumption of 'high fat' diet has received. Even though this LCD is high in fat, it is quite different in composition to what is commonly referred to as a 'high fat' diet. We have tried to compose a diet which has the nutrients required to achieve our goals, while maintaining a good taste in the meals. Our solution to the meal planning has been restricted because of the requirement to maintain a very low carbohydrate intake. However, there are many potential changes in the diet which may improve the taste and palatability while preserving the nutrient intake requirements.

We ask you to be as open-minded and objective as possible in your evaluation of the foods you are eating. We plan to use these comments as a basis for future improvements in the diet. You will be asked to provide evaluations of both the standard diet (STD) and the LCD on the same form while you are eating them. This scheme will allow us to more effectively evaluate the differences in your preferences for the two diets.

If you have any questions about the diets, instructions, or this questionnaire, please ask the investigator for further explanation.

Name: J. Doe (Subject #11) **APPENDIX B**

FOOD QUESTIONNAIRE

Date ___/___/___

(Please fill in the blanks or CIRCLE the BEST answer.)

Breakfast:

1. What TIME did you begin breakfast? _____

2. HOW HUNGRY were you when you began to eat?

   0. Not at all
   1. SLIGHTLY hungry
   2. MODERATELY hungry
   3. VERY hungry

3. Overall, did you get ENOUGH TO EAT?

   0. NOT enough
   1. Just the right amount
   2. TOO MUCH

4. Overall, how was the APPEARANCE of the meal?

   0. I did not ever see the meal
   1. The meal looked HORRIBLE
   2. The meal did NOT look VERY APPETIZING
   3. The meal looked SLIGHTLY UNAPPETIZING
   4. The meal looked OK (average appearance)
   5. The meal looked SLIGHTLY BETTER THAN AVERAGE
   6. The meal looked VERY GOOD
   7. The meal looked EXTREMELY DELICIOUS

Name: J. Doe (Subject #11) **APPENDIX B**

FOOD QUESTIONNAIRE

5. Overall, how did you like the TASTE of the meal?

   0. Did not eat any of the meal
   1. Disliked taste EXTREMELY
   2. Disliked taste MODERATELY
   3. Disliked taste SLIGHTLY
   4. The taste was OK (average)
   5. I liked taste SLIGHTLY BETTER than average
   6. I liked taste MUCH BETTER than average
   7. I thought the meal was TREMENDOUS (no improvements needed)

6. If there were any items which you PARTICULARLY LIKED, please note them below.

   0. There were No items which I PARTICULARLY LIKED.
   1. Yes, there were the following items which I PARTICULARLY LIKED

   ITEM(S) (Please list by name)

   _____
   _____
   _____
   _____

7. If there were any items which you particularly DID NOT LIKE, please note them below.

   0. No items were particularly bad
   1. Yes, there were the following items which I DID NOT LIKE

   ITEM(S) (Please list by name)

   _____
   _____
   _____
   _____

Name: J. Doe (Subject #11) **APPENDIX B**

FOOD QUESTIONNAIRE

8. IF you DID NOT EAT ALL of any item(s) provided in the meal, please note them below.

   0. I ate all of the food provided
   1. I did not eat any of the meal
   2. I did not eat ALL of the following items

ITEM(S)	AMOUNT ACTUALLY EATEN			
_____	None	1/4	1/2	3/4
_____	None	1/4	1/2	3/4
_____	None	1/4	1/2	3/4
_____	None	1/4	1/2	3/4
_____	None	1/4	1/2	3/4

9. Did you notice any physical problems within the next three hours after eating the meal?

   0. **NO PROBLEMS (Skip Question 10)**
   1. YES, I had the problems noted below **(Answer Question 10)**

10. IF you experienced problems (Question 9), circle those you noticed.

    a. Felt bloated or stuffed (too full)
    b. Indigestion or heartburn
    c. Gas
    d. Diarrhea
    e. Nausea
    f. Vomiting
    g. Cramps
    h. Very thirsty
    i. Other _____
       _____
       _____
       _____

Name: J. Doe (Subject #11) **APPENDIX B**

FOOD QUESTIONNAIRE

Lunch: (Same questions [1-10] as for Breakfast repeated)

Dinner: (Same questions [1-10] as for Breakfast repeated)

Summary:

A. What did you like MOST about the meals for the entire day?

_____

_____

_____

B. What did you like LEAST about the meals for the entire day?

_____

_____

_____

C. Do you have any suggestions for changes in the overall diet?

_____

_____

_____

D. What did you think about the SCHEDULE of the meals for the entire day?

0. I thought it was OK (three meals); NO CHANGES suggested.
1. I would rather have two meals (Breakfast and Dinner) with a snack between.
2. I would prefer to he only two meals (Breakfast & Dinner)
3. Other (please be specific).

_____

_____

_____

E. Do you have any additional comments not covered above?

1. NO additional comments.
2. YES:

_____

_____

_____

Name: J. Doe (Subject #11) **APPENDIX C**

DAILY DIARY

Date ___/___/___

STD or LCD Day #___

GENERAL QUESTIONS (covering entire day):

1. Use the following scale to rate how you felt during the day (at any time). Please fill in all blanks (Omitted answers will be assumed to be a '0'). Some questions may be repeated from above. Answer them again.

		POINTS
0.	**NO Problem**, I felt completely normal.	0
1.	SLIGHT symptom for PART of the day	0.5
2.	SLIGHT symptom for MOST or ALL of the day	2
3.	MODERATE symptom for PART of the day	1
4.	MODERATE symptom for MOST or ALL of the day	4
5.	SEVERE symptom for PART of the day	1.5
6.	SEVERE symptom for MOST or ALL of the day	6

SYMPTOMS: (You may have two answers to the same question: e.g., 5/2)

1. ____ Light-headed
2. ____ Headache(s)
3. ____ Dizzy
4. ____ Felt Faint
5. ____ Coordination was off
6. ____ Heart pounding
7. ____ Heart beating fast
8. ____ Muscle cramps
9. ____ Tight/stiff muscles
10. ____ Felt weak
11. ____ Felt sleepy
12. ____ Felt restless
13. ____ Felt irritable
14. ____ Felt sick to my stomach
15. ____ Had gas pressure
16. ____ My judgement was off
17. ____ Stomach ache
18. ____ Diarrhea
19. ____ Constipation
20. ____ Urinated MORE than Usual
21. ____ Urinated LESS than Usual
22. ____ Felt depressed
23. ____ I was forgetful
24. ____ My concentration was off
25. ____ Felt nervous or worried
26. ____ Lost my appetite
27. ____ Dry mouth
28. ____ My vision was NOT normal
29. ____ My energy level was down
30. ____ Couldn't sleep
31. ____ Felt chilly
32. ____ I didn't notice some things that I would normally
33. ____ More energy than normal.

Other Comments about how you felt? (Please be specific)_____

_____

_____

Name: J. Doe (Subject #11)

APPENDIX D

SAMPLE DIETS

Standard Diet (STD)	Low Carbohydate/High Fat Diet (LCD)
MONDAY	MONDAY
Breakfast	Breakfast
Apple juice (8 oz)	Whole Eggs (3)
Banana (1 med)	Cheddar cheese (45 gm)
Shredded Wheat (3/4 Cup)	Margarine (2 tbsp)
English Muffin (1)	English Muffin (1/2)
Margarine (1 tbsp)	Bacon (3 slices)
Whole Milk (8 Oz)	Diet jelly (1 packet)
Half & Half (2 tsp)	Decaf Coffee (8 oz)
Decaf Coffee (8 oz)	
Lunch	Lunch
Bologna Sandwich:	Hard boiled egg (1)
Bologna (3 oz)	Tuna, water pack (5 oz)
Mayonnaise (1 tbsp)	Mayonnaise (4 tbsp)
Bread (2 slices)	Mustard (1 tsp)
Fresh fruit (2 pieces)	Celery (80 gm)
Saltine crackers (6)	"Standard salad"
Margarine (2 tbsp)	Cream cheese (2.5 oz)
	Italian dressing (3 tbsp)
Dinner	Dinner
Cream of Vegetable Soup (6 oz)	Hamburger, 30% fat (120 gm)
Orange juice (8 oz)	Margarine (1 tsp)
Roast Turkey (3 oz)	Fried onions (80 gm)
Dressing (1/2 Cup)	"Standard salad"
Peas w/ mushrooms (1/2 Cup)	Avocado (80 gm)
Broccoli (1/2 Cup)	Oil & Vinegar Dressing:
Fresh Fruit (2 slices)	Oil (2 tbsp)
Dinner Roll (1)	Vinegar (1 tbsp)
Margarine (1 tbsp)	Sesame seeds (1 oz)
Half & half (2 tsp)	
Whole milk (12 oz)	
Decaf coffee (8 oz)	

ANALYSIS:

Kcals	3054	3004
Carbohydrate	48%	8%
Fat	35%	76%
Protein	14%	17%

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FIELD	GROUP	SUB GROUP	Diet, metabolism, triglycerides, insulin, glucose tolerance, low carbohydrate, cholesterol

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

(U) One of the principal metabolic adaptations to endurance training is an increase in the muscle's utilization of fat. This study investigated several components of metabolism during a three-week adaptation to a low (7-9%) carbohydrate/high (73-75%) fat diet (LCD) in man. Metabolic measurements were taken initially on ten healthy male volunteers, ages 19-41, who were on a maintenance exercise program while consuming a standard diet (STD) (50% carbohydrate/35% fat). These measurements were subsequently repeated after 7-11 and 17-21 days on the LCD. Questionnaires were administered on repeated occasions to evaluate food acceptability and subjective symptoms. The metabolic tests included intravenous glucose tolerance tests (GTT), meal response tests (MRT), and glucose/insulin clamps (CLAMP). Blood samples were also taken on several occasions during the STD and LCD periods to assess changes in overnight fasted blood glucose, free fatty acids, triglycerides, insulin, glucagon, cholesterol [total, high density lipoprotein (HDL), low density lipoprotein (LDL)], cortisol, thyroid hormone,
(Continued on reverse)

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19. Abstract (Continued)

electrolytes, and ketone bodies. The LCD was well-tolerated during the three-week adaptation period. The LCD produced lower blood triglycerides (-30%), glucose, thyroid hormone, and insulin/glucagon ratio. The LCD also elevated blood HDL-cholesterol, free fatty acids, and transiently elevated cortisol and ß-OH-butyrate. The MRT demonstrated markedly lower insulin, glucose, and triglyceride concentrations from consuming the LCD. The metabolic adaptation to the LCD resulted in unchanged insulin response to the GTT in the face of higher blood glucose during the test. The decrease in insulin sensitivity (glucose area/insulin area) indicated by the GTT was not confirmed by the CLAMP, which showed no change in insulin sensitivity. There was no change in muscle glycogen concentration after the three-week adaptation to the LCD. The alterations in metabolism demonstrated by this study are very encouraging for the use of the LCD as an adjunct to increasing certain types of exercise endurance, as well as for a potential treatment of several types of metabolic disorders.